REMARKS

Applicants wish again to thank Examiners Ann Lam and Long Lee for the cordial interview with one of the inventors, Jean I. Montagu, and John N. Williams, attorney of record, held on January 23, 2007, in respect of the companion patent application Serial number 11/431,997, a continuation of the present application. During the course of the interview aspects of the present invention and the present office action were also discussed, to which reference will be made in the course of these remarks.

The claims of the present application have been amended to form believed to be allowable over the art of record. In respect of the present rejection based on lack of unity, for reasons now to be explained, the linking apparatus claims of Group 1 are submitted to be allowable, thus making the unity issue moot. Accordingly it is requested that the requirement for restriction be withdrawn.

(To satisfy the requirement of the rules, provisionally, Group 1 is elected. Likewise, Applicant affirms the election referred to at the bottom of page 3 of the Office Action, while submitting that it, too, is moot, in view of the submitted allowability of the genus claims present in the application.)

The Present Invention

During the course of the January interview the role of substrates for quantitative assays of bio-material was discussed, as were the serious optical noise problem and low signal strength problem encountered when performing optical analysis using known substrate materials. As explained at the interview, and in detail in the specification, the inventors have found that significantly improved devices for immobilizing bio-material for quantitative bio-assays is achievable with thin coatings on rigid supports, in particular it being found that one or more adherent intervening layers between a rigid support and a coating of the substrate material combined with enhanced binding capability for the bio-material as the result of exposure of the surface of the thin coating to an energetic surface-altering treatment, can enable the achievement

of much improved quantitative analysis. While the thinness of the coating enables production of less background noise, production of the coatings with highly uniform thickness enabled by the one or more adherent intervening layers between the rigid support and the coating permits the remaining background signal to be efficiently subtracted from the signal obtained from the material being assayed, while the energetic surface treatment of the coating surface enables tenacious retention of bio-material by the surface of the coating during fluid flows of the assay, thus leading to large signal from tags attached to the bio-material being analyzed . Thus the combination of features leads to unusually effective quantitative assays.

The broadest aspect of this invention is set forth in amended claim 79: a device constructed for immobilizing a bio-material capable of becoming associated with a fluorophore tag or luminescent tag for optical emission analysis, comprising a coating of a polymer capable of binding with the bio-material, the coating having a thickness less than about 5 micron, the coating of polymer adhered to a rigid support via one or more adherent intervening layers, the coating of polymer having an outer deposit-receiving surface that has enhanced binding capability for the bio-material as the result of exposure of the surface to an energetic surface-altering treatment, and a deposit of the bio-material immobilized on the treated surface of the polymer coating.

The other claims bring out very important detailed features that enable superior results in many cases. For instance:

Independent claim 55 requires the coating to be nitrocellulose; Independent claim 51 requires the nitrocellulose coating to overlie an intervening layer of metal oxide and for its surface to be corona treated; Independent claims 118 and 119 with varying particularity require the intervening layer(s) to be opaque; Dependent claim 104 calls for the coating to be comprised of nitrocellulose polymer or polystyrene polymer that is ultra-thin, having a thickness t_{ot} less than about 3 micron, and independent claim 120 as well as dependent claim 104 require the treated surface to be the result of exposure of the outer surface of the polymer coating to at least one of corona treatment, flame treatment, bombardment by charged particles comprising electrons, ions or sub-atomic particles, or electromagnetic radiation of ultraviolet, gamma or X-ray wavelength,

with the coating carrying a deposit of protein bio-material or cellular bio-material. These and other important detailed features are presented elsewhere in claims of the claim set.

It is pointed out that it is important for proper protection of the present invention to employ a "product by process" limitation such as: that the coating of polymer have "an outer deposit-receiving surface that has enhanced binding capability for the bio-material as the result of exposure of the surface to an energetic surface-altering treatment", or that "the treated surface... be the result of exposure of the outer surface of the polymer coating to at least one of corona treatment, flame treatment, bombardment by charged particles comprising electrons, ions or sub-atomic particles, or electromagnetic radiation of ultraviolet, gamma or X-ray wavelength", or, specifically, that the surface be "corona-treated" or subjected to gamma radiation.

These treatments, while varying in physical detail as to their effects as noted in the specification, have, in common, improved binding capability for bio-material, relative to the native coating substance.

The Examiner's grounds for rejection in the Office Action, page 4 at bottom, is that "...[T]here is no indication that such treatment would make a surface different from that disclosed by Brigati [i.e. plain, untreated solid nitrocellulose layer]".

It is submitted that by examination of the specification, this clearly is not correct. Alteration of the surface as evidenced by improved binding and immobilization is clearly disclosed in the following passages of the specification:

Page 7, lines 18-21: "It has also been realized that such ultra-thin substrates[i.e. coatings with thickness less than 5 micron] may be altered after forming as a coating..., as by corona discharge, atomic particle or radiation bombardment or by controlled energy excimer laser beam treatment, to improve binding and immobilization topology or conditions."

Page 18, line 23 to page 19, line 2: There is "...[A]n additional aspect of the invention, the modification of the surface of polymer substrate films, such as nitrocellulose or polystyrene, to enhance affinity or binding properties for the biomaterial or molecules. The modification may be to change the topology, the chemical nature or the charge state of the surface. ....Surface modification conditions to enhance the binding affinity of the surface to biological molecules such as protein or DNA or....can be corona treatment, flame treatment, or bombardment as with ions, electrons or atomic or sub-atomic particles or radiation including gamma rays or X-rays."

Page 37, lines 21-27: "Following the above steps [of forming the nitrocellulose layer] the slides are subsequently washed and, as shown in Fig. 12, exposed to surface treatment to promote adhesion properties of the film or membrane. During corona treatment, the slide 100 is translated under a jet of reactive species,124, e.g. ozone, produced by a corona treater...If electromagnetic radiation such as ultraviolet light is utilized, a suitable source of photons is used to process the surface, e.g. a UV laser beam...".."

Page 39, line 13 et seq: "...[T]he slides are subjected to a surface modification with corona treatment (see Fig. 12)...."

Further, during the course of the interview of the companion application, to which the Examiner is referred, Mr. Montagu described experiments with corona treatment and exposure to gamma radiation that confirm that a significant difference in binding capability is attainable by such treatment.

Claim Rejections-35 USC Section 102

Claims 51, 55-61, 72-75, 79-82, 85, 86, 89-92 104-111 were rejected as being anticapted by Brigati, EPO 0366241.

It is clear, in view of the amendments and the explanation above that this rejection is erroneous. Brigati has no teaching whatsoever of the claimed surface treatment! Nor, as will be discussed further below, does Brigati employ an adherent intervening layer beneath a thin coating!

Indeed, whereas Brigati's preferred thickness range was about 10 to about 30 micron, applicants achieve superior results for their purposes near or below the minimal Brigati range, i.e. less than 5 micron, 3 micron or, preferably 1 micron. Clearly this is because of the added features, not found in Brigati, and apparently unobvious to him.

(The Examiner will recall, at the recent interview it was pointed out that Brigati is directed to defining a capillary gap between coated members carrying biology. It was submitted that Brigati has no fair disclosure related to the fluorescence background problem addressed by the claims of the present application. Col. 8, lines 33-36 of Brigati was brought to the attention of the Examiners: "In general, adsorbent polymer layers [nitrocellulose is disclosed] should have a thickness of about 2 to about 50um, preferably about 5 to about 50 um and more preferably about 10 to about 30 um." [Emphasis ours])

Adherent Intervening Layer Between Rigid Support and Coating Not Disclosed by Brigati

As mentioned above, by use of at least one adherent intervening layer, the uniformity of the coating of less than about 5 micron thickness or thinner can be enhanced and the coating enabled to better endure the rigors of pin or other spotting, multi-step assays and handling.

In rejecting claim 111, the Examiner said further of Brigati that "[A]n adhesive applied between the nitrocellulose and glass surface (col. 9, lines 5-15) is considered to be the intervening layer ...", office action page 5, lines 3,4.

In this statement the Examiner is apparently referring to the passage:

> If a continuous nitrocellulose layer is applied from solution (as described below), then it is preferred that its thickness be kept small enough for the gap to be at least 150 um thick (that is a thickness of layer 213 in this embodiment of 30 um or

less). Nitrocellulose layer could, however, be a thin filter layer applied directly to surface 212 with an adhesive or otherwise. In the event that a 50 um thick layer was applied in this fashion, the gap thickness would be 130 um, which would still be suitable for many applications. Col. 9, lines 7-18.

It is pointed out that the text above, as an alterative to coating from a solution, refers to applying a layer or a 50 micron thick nitrocellulose "filter layer" directly to surface 212 "with an adhesive" 50. In other words, rather than refer to a coating (to which all present claims are limited) Brigati refers to gluing down preformed nitrocellulose filter material. Of course, filter material is common to the biotech field, see for instance those materials shown in Exhibit B, attached to Mr. Montagu's declaration in the companion application. It is submitted, therefore, that the cited passage refers to adhesively joining a preformed layer to a support, and does not teach use of an adherent intermediate layer upon which a thin coating is being formed, e.g., by coating with a polymer coating solution, as required by all the claims.

In particular Brigati does not teach an adherent intervening layer as a technique to achieve best operations at thicknesses at his extreme,non-preferred thickness range or below!

For both these reasons it is submitted that Brigati does not anticipate any of the claims as now presented.

Claim Rejections-35 USC Section 103

Claims 53, 54, 87, 88, 104 and 116 were rejected as being unpatentable over Brigati in view of McMahon et al, 5,310,650.

Brigati has already been adequately discussed.

As explained at the interview and in the companion application, the "in view of" reference, McMahon et al., was cited by the Examiner because of its disclosure in Example 1 of "0.45 micron". It is pointed out that interpreting this to refer to **thickness** is incorrect. Attention is called to the disclosure of McMahan et al., in regard to thickness: "[T]hickness in the range of from about 0.01 mm [i.e. 10 micron] to about 0.5 [500 micron], with preferred thickness of 0.1

mm [100 micron].", Column 8, lines 25-27. Example 5, McMahon et al. discloses "0.45" as relating to porosity (not thickness) of the material:

> "In this example, a single pathway polynucleotide hybridization assay devices were constructed of microporous (0.45 micron) nitrocellulose material approximately 5 mm wide by 55 mm long with a thickness of approximately 0.1 mm." (Column 17, lines 24-28)

In relation to pore size the McMahon reference defines the range as follows:

> "The pore size may vary within wide limits but is preferably between about 0.20 micron and 10 microns, especially between about 1 micron and 8 microns and most preferably 5 microns." (Column 8, lines 3-7)

See also McMahon et al. claim 2 "a strip of nitrocellulose having a pore size between about 0.2 micron and about 10 microns," and claims 2, 13, 22 and 31 requiring porosity range between about 0.1 micron and about 10 microns.

The importance of porosity to the McMahon et al. disclosed capillary action in the gap is explained by McMahon et al.:

> "As pore size increases, flow rate and kinetics also increase at the expense of hybridization efficiency and binding capacity. A most preferred medium is Schleicher & Schuell (Keene N.H.) nitrocellulose having a pore size of 5.0 microns." (Column 8, lines 10-14)

It is submitted to be clear that the disclosure of "0.45 micron" in McMahon, et al. Example 1, to which the office actions refers: i.e. "A sheet of 0.45 micron nitrocellulose membrane, Schleicher & Schuell, Keene, N.H.", Column 11, lines 67, 68), refers only to the dimension of the pores in a porous membrane; clearly "0.45" is not disclosed as thickness of the McMahon porous membrane. See also Exhibit B to the declaration by Mr. Montagu in the companion application.

McMahon has no disclosure of coatings of thickness less than about 5 micron and below!

In summary, the inventions of the rejected claims, and all others , were not known or made obvious to those in the field by Brigati or McMahon or any proper combination of their teachings. The rejection should be withdrawn.

Claims 76-78 and 119 were rejected based on both the references above, further in view of Richardson 6, 381,013, while claims 62, 63, 65-68, 70, 83, 84, 93, 94, 112-114, 118, 120 were rejected over Brigati in view of Richardson.

Brigati and Richardson have already been adequately discussed.

The Examiner's position regarding Richardson, page 7, is that:

> Richardson teaches that where it is desired to use a slide in the UV portion of the spectrum, a UV contrast enhancement for the slide can comprise thin films or tantalum oxide or other suitable materials as will occur to those of skill in the art (col. 7, lines 46-65). It would have been obvious to one of ordinary skill in the art at the time the invention was made to provide a tantalum oxide film on the Brigati slide because Richardson teaches that such a film provides the benefit of UV contrast enhancement, as would be desirable where UV portion of the spectrum is used for analysis. Tantalum oxide is substantially opaque (as is disclosed by Applicants in the specification).

Richardson Does Not Teach an Adherent Intervening Layer for the Bio-material Supporting Coating

As already noted, the cited passages of Brigati and McMahon do not teach an adherent intervening layer for adhering a bio-material-receiving coating of less than 5 micron thickness to a rigid base. Furthermore, Richardson 6,318,013 does not teach tantalum oxide as an intervening adherent layer for anything, and certainly not as a way to obtain durable, continuous coatings of such minimal thickness on a rigid support for bio-material asxsays. Claims so limited should be allowed over this reference.

In regard to the above-quoted comments from the office action, it is also noted that immunoassays are excited and read in the visible (not UV) spectrum. It is believed there are no fluorescence-based assays conducted with ultra violet light because polymer substrates exhibit extreme auto-fluorescence when exposed to such wavelengths.

Richardson Does Not Teach Opacity to Block Optical Background Noise from the Rigid Support in Conducting Optical Assays.

Not only do the coatings of less than 5, or 3 or preferably 1 micron provide low, lower and advantageously very low optical background noise. By providing substantial opacity below the coating, noise is deterred from reaching the detector from the rigid support, i.e. noise, such as auto-fluorescence from a glass or plastic support, as might occur as a result of illumination or fluorophore-stimulating radiation.

Claims directed to this feature were rejected as being unobvious over Brigati in view of Richardson 6,381,013, noted above.

Richardson teaches, for calibrating a microscope, a contrast layer for **reference images** on a reference slide when viewed in **UV (ultraviolet)**. Richardson has no teaching for improving quantitative detection of signal in the visible spectrum during assays of deposits bound to the top surface of a solid nitrocellulose coating, by making substantially opaque the portion of the device below the coating and especially does not teach that an adherent intervening layer be opaque, or to make such layer of tantalum oxide, to achieve uniform, stable, and durable thin coatings that may have this useful opacity.

Therefore, claims directed to this use of opacity generally and to substantially opaque intervening adherent coatings are submitted to be allowable in their own right over the cited references.

Further features in the claims, though not discussed here, are important as previously explained to the Examiner and are basis for allowance in their own right.

Conclusion

When an assay is conducted with devices claimed and the results examined by optical analysis, the coating is found to successfully maintain immobilization of the bio-material after exposure to liquid during the assay. When illuminated for optical analysis, marked advantage is achieved of low auto-fluorescence noise attributable to the coating and improved quantitiative measurements attributable to the uniformity of the coating, and the considerable size of the signal due to the amount of bio-material immobilized by it.

All aspects of invention claimed here are important and believed to be clearly allowable over the prior art of record as claimed.

Upon indication of allowable subject matter, Applicant offers to submit a terminal disclaimer in the Present Application in respect of the companion application.

Because of Allowability of the base claims rejoinder and allowance of the restricted claims is requested.

For the reasons given, all pending claims are submitted to patentably distinguish all prior art of record and early favorable action is solicited.

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Enclosed is a $1675.00 check for excess claim fees. Please apply any other charges or credits to deposit account 06-1050, referencing Attorney Docket No. 13165-004US1.

Respectfully submitted,

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John N. Williams
Reg. No. 18,948

Fish & Richardson P.C.
225 Franklin Street
Boston, MA 02110
Telephone: (617) 542-5070
Facsimile: (617) 542-8906